Manuscript Title: A Public Health Perspective on 21st Century Risk Assessment

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Abstract

Preventing adverse health impacts from exposures to environmental chemicals is fundamental to protecting individual and public health. When done efficiently and properly, chemical risk assessment enables risk management actions that minimize the incidence and impacts of environmentally-induced diseases related to chemical exposure. However, traditional chemical risk assessment is faced with multiple challenges with respect to predicting and preventing disease in human populations, and epidemiological studies increasingly report observations of adverse health effects at exposure levels predicted from animal studies to be safe for humans. This discordance reinforces concerns about the adequacy of contemporary risk assessment practices [ADDIN EN.CITE <EndNote><Cite><Author>Birnbaum</Author><Year>2016</Year><RecNum>14</RecNum><DisplayText>(Birnbaum, Burke, & Jones, 2016)</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468526461">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Linda S. Birnbaum</author><author>Thomas A. Burke</author><author>James J. Jones</author></authors></contributors><titles><title>Informing 21st-Century Risk Assessments with 21st-Century Science</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>A60-A63</pages><volume>124</volume><number>4</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] for protecting public health. It is becoming clear that to protect public health more effectively, future risk assessments will need to use the full range of available data, draw on innovative methods to integrate diverse data streams, and consider health endpoints that also reflect the range of subtle effects and morbidities observed in human populations. Given these factors, there is a need to reframe chemical risk assessment to be more clearly aligned with the public health goal of minimizing environmental exposures associated with disease.

Overview

For the past several decades, human health risk assessment has been a pillar of environmental health protection. In general, the products of risk assessment have been numerical risk values derived from animal toxicology studies of observable effects at high doses of individual chemicals. While this approach has contributed to our understanding of overt health outcomes from chemical exposures, it does not always match our understanding from epidemiology studies of the consequences of real world exposures in human populations, which are characterized by exposure to multiple pollutants, often chronically, at concentrations that can fluctuate over wide ranges; susceptible populations and lifestages; potential interactions between chemicals and nonchemical stressors and background disease states; and lifestyle factors that modify exposures (e.g., air tight houses).

Ten years ago, the National Research Council (NRC) offered a new paradigm for evaluating the safety of chemicals based on chemical characterization, testing using a toxicity pathway approach, and modeling and extrapolating the dose-response relationship from *in vitro* testing, all embedded in a risk context and considering population-based data and exposure [ADDIN EN.CITE <EndNote><Cite><Author>National Research Council</Author><Year>2007</Year><RecNum>10</RecNum><DisplayText>(National Research Council, 2007)</DisplayText><record><rec-number>10</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468525960">10</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>National Research Council,</author></authors><tertiary-authors><author>The National Academies Press,</author></tertiary-authors></contributors><titles><title>Toxicity Testing in the 21st Century: A Vision and a Strategy</title></titles><dates><year>2007</year></dates><pub-location>Washington, D.C.</pub-location><urls></urls></record></Cite></EndNote>]. Efforts such as the Tox21 consortium [ADDIN EN.CITE <EndNote><Cite><Author>Kavlock</Author><Year>2009</Year><RecNum>11</RecNum><DisplayText>(R. J. Kavlock, Austin, & Tice, 2009; Tice, Austin, Kavlock, & Bucher, 2013)</DisplayText><record><rec-number>11</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468526016">11</key></foreign-

keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Robert J. Kavlock</author><author>Christopher P. Austin</author><author>Raymond Tice</author></authors></contributors><titles><title>Toxicity Testing in the 21st Century: Implications for Human Health Risk Assessment</title><secondary-title>Risk Anal</secondary-title></titles><periodical><full-title>Risk Anal</full-title></periodical><pages>485-497</pages><volume>29</volume><number>4</number><dates><year>2009</year></dates><urls></urls></record></Cite><Cite><Author>Tice</Author><Year>2013</Year><RecNum>5</RecNum><record><rec-number>5</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468525644">5</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Raymond R. Tice</author><author>Christopher P. Austin</author><author>Robert J. Kavlock</author><author>John R. Bucher</author></authors></contributors><titles><title>Improving the Human Hazard Characterization of Chemicals: A Tox21 Update</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>756-765</pages><volume>121</volume><number>7</number><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>] and ToxCast program [ADDIN EN.CITE <EndNote><Cite><Author>Kavlock</Author><Year>2012</Year><RecNum>19</RecNum><DisplayText>(R. Kavlock et al., 2012)</DisplayText><record><rec-number>19</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468527616">19</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Robert Kavlock</author><author>Kelly Chandler</author><author>Keith Houck</author><author>Sid Hunter</author><author>Richard Judson</author><author>Nicole Kleinstreuer</author><author>Thomas Knudsen</author><author>Matt Martin</author><author>Stephanie Padilla</author><author>David Reif</author><author>Ann Richard</author><author>Daniel Rotroff</author><author>Nisha Sipes</author><author>David Dix</author></authors></contributors><titles><title>Update on

EPA's ToxCast Program: Providing High Throughput Decision Support Tools for Chemical Risk Management</title><secondary-title>Chem Res Toxicol</secondary-title></titles><periodical><full-title>Chem Res Toxicol</full-title></periodical><pages>1287-1302</pages><volume>25</volume><number>7</number><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>] have helped us better understand the biological interactions of large numbers of chemicals using high-throughput assay systems, and we are witnessing early adoption of new technologies and approaches for screening chemicals for integrated testing [ADDIN EN.CITE <EndNote><Cite><Author>Browne</Author><Year>2015</Year><RecNum>18</RecNum><DisplayText>(Browne, Judson, Casey, Kleinstreuer, & Thomas, 2015)</DisplayText><record><rec-number>18</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468527458">18</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Patience Browne</author><author>Richard S. Judson</author><author>Warren M. Casey</author><author>Nicole C. Kleinstreuer</author><author>Russell S. Thomas</author></authors></contributors><titles><title>Screening Chemicals for Estrogen Receptor Bioactivity Using a Computational Model</title><secondary-title>Environmental Science & Technology</secondary-title></titles><periodical><full-title>Environmental Science & Technology</full-title></periodical><pages>8804-8814</pages><volume>49</volume><number>14</number><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>].

Several other factors are also changing the way environmental health professionals think about chemical risks and how to most effectively protect public health. It is estimated that intrinsic factors (e.g., those that result in mutations due to random errors in DNA replication) account for only 10-30% of many common cancers [ADDIN EN.CITE <EndNote><Cite><Author>Wu</Author><Year>2016</Year><RecNum>20</RecNum><DisplayText>(Wu, Powers, Zhu, & Hannun, 2016)</DisplayText><record><rec-number>20</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs"

timestamp="1470317090">20</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Song Wu</author><author>Scott Powers</author><author>Wei Zhu</author><author>Yusuf A. Hannun	</author></authors></contributors><titles><title>Substantial contribution of extrinsic risk factors to cancer development</title><secondary-title>Nature</secondary-title></titles><periodical><full-title>Nature</full-title></periodical><pages>43-47</pages><volume>529</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. Similarly, only 30-40% of birth defects can be attributed to known causes such as genetics, fetal alcohol syndrome, maternal smoking, and folate insufficiency [ADDIN EN.CITE <EndNote><Cite><Author>Weinhold</Author><Year>2009</Year><RecNum>3</RecNum><DisplayText>(Weinhold, 2009)</DisplayText><record><rec-number>3</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468525478">3</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>B. Weinhold</author></authors></contributors><titles><title>Environmental Factors in Birth Defects: What We Need to Know</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>A440-A447</pages><volume>117</volume><number>10</number><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. Other studies have concluded that non-genetic environmental factors and gene by environment interactions are the primary causes of chronic diseases [ADDIN EN.CITE <EndNote><Cite><Author>Rappaport</Author><Year>2011</Year><RecNum>21</RecNum><DisplayText>(Rappaport, 2011; Rappaport, Barupal, Wishart, Vineis, & Scalbert, 2014)</DisplayText><record><rec-number>21</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470317192">21</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Stephen M.

Rappaport</author></authors></contributors><titles><title>Implications of the exposome for exposure science</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><pages>5-9</pages><volume>21</volume><dates><year>2011</year></dates><urls></urls></record></Cite><Cite><Author>Rappaport</Author><Year>2014</Year><RecNum>22</RecNum><record><rec-number>22</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470317303">22</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Stephen M. Rappaport</author><author>Dinesh K. Barupal</author><author>David Wishart</author><author>Paolo Vineis</author><author>Augustin Scalbert</author></authors></contributors><titles><title>The Blood Exposome and Its Role in Discovering Causes of Disease</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>769-774</pages><volume>122</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. The ability to evaluate and quantify the role of environmental factors on public health is a clear opportunity, but it is limited by the lack of readily available models for prominent clinical outcomes.

Current challenges in predicting risk from exposure to environmental chemicals

Understanding public health risk from environmental chemical exposures is complicated by many factors, such as population variability and susceptibility, which are poorly understood and difficult to characterize and incorporate into risk assessments. For example, a person's unique microbiome may modulate his/her response to environmental exposures [ADDIN EN.CITE <EndNote><Cite><Author>Dietert</Author><Year>2015</Year><RecNum>25</RecNum><DisplayText>(Dietert & Silbergeld, 2015; Patterson & Turnbaugh, 2014)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470317694">25</key></foreign-

keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rodney Reynolds Dietert</author><author>Ellen Kovner Silbergeld</author></authors></contributors><titles><title>Biomarkers for the 21st Century: Listening to the Microbiome</title><secondary-title>Toxicological Sciences</secondary-title></titles><periodical><full-title>Toxicological Sciences</full-title></periodical><pages>208-216</pages><volume>144</volume><number>2</number><dates><year>2015</year></dates><urls></urls></record></Cite><Cite><Author>Patterson</Author><Year>2014</Year><RecNum>24</RecNum><record><rec-number>24</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470317566">24</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Andrew D. Patterson</author><author>Peter J. Turnbaugh</author></authors></contributors><titles><title>Microbial Determinants of Biochemical Individuality and Their Impact on Toxicology and Pharmacology</title><secondary-title>Cell Metabolism</secondary-title></titles><periodical><full-title>Cell Metabolism</full-title></periodical><pages>761-768</pages><volume>20</volume><number>5</number><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. Although studies are limited in this emerging area, knowledge about the microbiome may inform interindividual variability and unexplained susceptibility observed in populations. Scientists have begun to appreciate the role of the microbiome in the lack of reproducibility and interpretability of animal studies [ADDIN EN.CITE <EndNote><Cite><Author>Servick</Author><Year>2016</Year><RecNum>43</RecNum><DisplayText>(Servick, 2016)</DisplayText><record><rec-number>43</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472143865">43</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kelly Servick</author></authors></contributors><titles><title>Of mice and microbes</title><secondary-title>Science</secondary-title></titles><periodical><full-title>Science</full-title></periodical><pages>741-743</pages><volume>353</volume><number>6301</number><dates><year>2016</year></d

ates><urls></urls></record></Cite></EndNote>]. Other examples of important factors to incorporate in risk assessments can be found in Table 1.

Opportunities for leveraging multiple data types for public health protection

Concurrent with these challenges, science and technology are advancing rapidly and in ways that create opportunities for risk assessment. Public health disciplines help us understand how baseline health status can influence the impact of population level chemical exposures. We also need to consider how environmental pollutants may contribute to overall disease burden for endpoints not traditionally considered in chemical risk assessment (e.g., metabolic disorders). New methods in epidemiological research help us evaluate complex interactions among multifactorial causes of disease ranging from macro (societal, neighborhood) to micro (molecular) factors, relevance of exposures during sensitive lifestages, and a better understanding of interrelatedness of disease across lifespan [ADDIN EN.CITE <EndNote><Cite><Author>Louis</Author><Year>2015</Year><RecNum>27</RecNum><DisplayText>(Louis et al., 2015)</DisplayText><record><rec-number>27</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470317909">27</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Germaine M. Buck Louis</author><author>Michael S. Bloom</author><author>Nicolle M. Gatto</author><author>Carol R. Hogue</author><author>Daniel J.Westreich</author><author>Cuilin Zhang</author></authors></contributors><titles><title>Epidemiology's Continuing Contribution to Public Health: The Power of "Then and Now"</title><secondary-title>American Journal of Epidemiology</secondary-title></titles><periodical><full-title>American Journal of Epidemiology</full-title></periodical><pages>e1-e8</pages><volume>181</volume><number>8</number><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>]. Advances in high-throughput technologies and computational modeling (e.g., ToxCast, Tox21, and ExpoCast efforts) are providing data on hazard and exposure potential for a large number of data-poor chemicals. One approach with potential to advance our understanding of how chemical exposures can impact health is the use of adverse

outcome pathways (AOPs), which integrate various types of biological information to link molecular initiating events to downstream key events and ultimately unwanted health outcomes [ADDIN EN.CITE ADDIN EN.CITE.DATA]. To fully realize the potential of AOP-based approaches and to integrate biological findings across disciplines, we must strengthen our ability to detect precursor events in human populations and identify biologically-relevant exposure metrics, ideally measurable in individuals.

Effectively predicting population risk by integrating a variety of data streams (e.g., epidemiology, toxicology, high-throughput testing) and considering multiple sources and pathways of exposure can better inform environmental public health decisions. Advances in technology and computational capabilities have fostered new opportunities for generating and analyzing molecular, animal, and human data on effects and exposures, which can be integrated into chemical risk assessments. At the same time, probabilistic and high-throughput approaches for risk assessment have been advancing. Table 2 highlights various data types available and challenges applying these data types to inform risk assessment.

A public health perspective for chemical risk assessment

A public health perspective for chemical risk assessment would approach risk assessment from a new lens. It would address population health with a focus on health and societal burden of disease; use and integrate all available types of data – including traditional toxicology, human epidemiological findings, as well as newer and emerging data streams and information, such as digital epidemiology [ADDIN EN.CITE <EndNote><Cite><Author>Bakker</Author><Year>2016</Year><RecNum>47</RecNum><DisplayText>(Bakker, Martinez-Bakker, Helm, & Stevenson, 2016; Salathé et al., 2012)</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472144804">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kevin M. Bakker</author><author>Micaela Elvira Martinez-Bakker</author><author>Barbara Helm</author><author>Tyler J. Stevenson</author></authors></contributors><titles><title>Digital epidemiology reveals global

childhood disease seasonality and the effects of immunization</title><secondary-title>PNAS</secondary-title></titles><periodical><full-title>PNAS</full-title></periodical><pages>6689-6694</pages><volume>113</volume><number>24</number><dates><year>2016</year></dates><urls></urls></record></Cite><Cite><Author>Salathé</Author><Year>2012</Year><RecNum>46</RecNum><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472144671">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Marcel Salathé</author><author>Linus Bengtsson</author><author>Todd J. Bodnar</author><author>Devon D. Brewer</author><author>John S. Brownstein</author><author>Caroline Buckee</author><author>Ellsworth M. Campbell</author><author>Ciro Cattuto</author><author>Shashank Khandelwal</author><author>Patricia L. Mabry</author><author>Alessandro Vespignani </author></authors></contributors><titles><title>Digital Epidemiology</title><secondary-title>PLoS Comput Biol</secondary-title></titles><periodical><full-title>PLoS Comput Biol</full-title></periodical><pages>e1002616</pages><volume>8</volume><number>7</number><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>], high-throughput data, and adverse outcome pathways; and draw on public health approaches, such as attributable risk or relative risk. This new perspective may be especially important for some historically challenging aspects of risk assessment, such as understanding cumulative risks of exposures to multiple chemical and non-chemical stressors. Internationally, scientists have raised concerns about the large number of ubiquitous chemicals people are exposed to and called for rethinking approaches to evaluating the health impacts of chemicals (Goodson et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] Bennett et al. 2016). Figure 1 presents a conceptual model for a public health perspective for risk assessment.

While approaching assessments from the perspective of health outcomes may be challenging, it provides the opportunity to evaluate exposures and effects across the lifespan that are relevant to population health. Advances in science and technology – such as AOP development (OECD

website), the broader availability of chemical and biological data, and the applications of statistical and bioinformatics tools bring this previously aspirational approach well within reach [ADDIN EN.CITE <EndNote><Cite><Author>Rom</Author><Year>2013</Year><RecNum>49</RecNum><DisplayText>(Rom, Boushey, & Caplan, 2013)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472145433">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>William N. Rom</author><author>Homer Boushey</author><author>Arthur Caplan</author></authors></contributors><titles><title>Experimental Human Exposure to Air Pollutants Is Essential to Understand Adverse Health Effects</title><secondary-title>Am J Respir Cell Mol Biol</secondary-title></titles><periodical><full-title>Am J Respir Cell Mol Biol</full-title></periodical><pages>691-696</pages><volume>49</volume><number>5</number><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>].

Illustrative Example: Cardiovascular Disease

The following example illustrates how a public health approach may inform the challenge of cardiovascular disease. Cardiovascular disease is the number one cause of mortality worldwide and is a major U.S. public health burden [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Annual costs of cardiovascular disease in the U.S. were estimated to be $317 million in 2011-2012, considering direct medical costs and lost productivity due to premature mortality (Mozaffarian et al., 2016). This estimate is likely to substantially underestimate the social cost of cardiovascular disease, due to limitations in estimation of indirect costs associated with morbidity and premature mortality (U.S. EPA 2010). While much is known about the biochemical and behavioral risk factors associated with cardiovascular disease, particularly in comparison with other diseases and health conditions, the traditional risk factors fail to account for 10 to 25 percent of its prevalence [ADDIN EN.CITE <EndNote><Cite><Author>Kannel</Author><Year>2009</Year><RecNum>13</RecNum><Displ

ayText>(Kannel & Vasan, 2009)</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468526291">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>William B. Kannel</author><author>Ramachandran S. Vasan</author></authors></contributors><titles><title>Adverse Consequences of the 50% Misconception</title><secondary-title>Am J Cardiol</secondary-title></titles><periodical><full-title>Am J Cardiol</full-title></periodical><pages>426-427</pages><volume>103</volume><number>3</number><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. Environmental factors including air pollution [ADDIN EN.CITE <EndNote><Cite><Author>Kaufman</Author><Year>2016</Year><RecNum>12</RecNum><DisplayText>(Kaufman et al., 2016)</DisplayText><record><rec-number>12</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468526230">12</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Joel D Kaufman</author><author>Sara D Adar</author><author>R Graham Barr</author><author>Matthew Budoff</author><author>Gregory L Burke</author><author>Cynthia L Curl</author><author>Martha L Daviglus</author><author>Ana V Diez Roux</author><author>Amanda J Gassett</author><author>David R Jacobs Jr</author><author>Richard Kronmal</author><author>Timothy V Larson</author><author>Ana Navas-Acien</author><author>Casey Olives</author><author>Paul D Sampson</author><author>Lianne Sheppard</author><author>David S Siscovick</author><author>James H Stein</author><author>Adam A Szpiro</author><author>Karol E Watson</author></authors></contributors><titles><title>Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study</title><secondary-title>The Lancet</secondary-title></titles><periodical><full-title>The Lancet</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNot

e>] and chemical exposures [ADDIN EN.CITE <EndNote><Cite><Author>Kirkley</Author><Year>2014</Year><RecNum>53</RecNum><DisplayText>(Kirkley & Sargis, 2014)</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472146476">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Andrew G. Kirkley</author><author>Robert M. Sargis</author></authors></contributors><titles><title>Environmental Endocrine Disruption of Energy Metabolism and Cardiovascular Risk</title><secondary-title>Curr Diab Rep</secondary-title></titles><periodical><full-title>Curr Diab Rep</full-title></periodical><pages>494</pages><volume>14</volume><number>6</number><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>] are thought to contribute to the unexplained fraction. While mortality due to cardiovascular disease has decreased over the last few decades in the developed world due to reductions in behavioral risk factors, the rising prevalence of obesity and diabetes might account for the deceleration in the rate of improvement in annual cardiovascular mortality in the U.S. over the last few years [ADDIN EN.CITE <EndNote><Cite><Author>Sidney</Author><Year>2016</Year><RecNum>54</RecNum><DisplayText>(Sidney, Quesenberry et al. 2016)</DisplayText><record><rec-number>54</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472146661">54</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sidney, S</author><author>Quesenberry,, Jr., CP</author><author>Jaffe, MG</author><author>Sorel, M</author><author>Nguyen-Huynh, MN</author><author>Kushi, LH</author><author>Go, AS</author><author>Rana, JS</author></authors></contributors><titles><title>Recent Trends in Cardiovascular Mortality in the United States and Public Health Goals</title><secondary-title>JAMA Cardiol</secondary-title></titles><periodical><full-title>JAMA Cardiol</full-title></periodical><pages>594-599</pages><volume>1</volume><number>5</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].

There is an urgent need to better understand the biological pathways through which environmental exposures to chemical and non-chemical stressors act to stimulate and accelerate atherosclerosis and promote adverse cardiovascular health effects. Applying the adverse outcome pathway framework [ADDIN EN.CITE <EndNote><Cite><Author>Cosselman</Author><Year>2015</Year><RecNum>35</RecNum><DisplayText>(Cosselman, Navas-Acien, & Kaufman, 2015)</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470320174">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kristen E. Cosselman</author><author>Ana Navas-Acien</author><author>Joel D. Kaufman</author></authors></contributors><titles><title>Environmental factors in cardiovascular disease</title><secondary-title>Nature Reviews Cardiology</secondary-title></titles><periodical><full-title>Nature Reviews Cardiology</full-title></periodical><pages>627-642</pages><volume>12</volume><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>], the initial molecular response to a chemical exposure will often be receptor activation and changes in metabolism, and ultimately changes in tissue and organ function. Such changes can be modified by both intrinsic (e.g., sex, age, genetic and epigenetic background) and extrinsic factors (e.g., co-exposures to other chemical and non-chemical stressors). Over time, these changes produce subclinical effects such as changes in electrical and mechanical cardiac function, vascular function, and non-obstructive atherosclerotic vascular changes. With persistence of metabolic changes that stimulate the progression of vascular disease, clinical cardiovascular events such as heart attacks, strokes, heart failure, and abnormal heart rhythms follow.

To date, the most comprehensive application of this approach has been in the study of population level health effects of air pollution exposure [ADDIN EN.CITE <EndNote><Cite><Author>Cosselman</Author><Year>2015</Year><RecNum>35</RecNum><DisplayText>(Cosselman et al., 2015)</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs"

timestamp="1470320174">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kristen E. Cosselman</author><author>Ana Navas-Acien</author><author>Joel D. Kaufman</author></authors></contributors><titles><title>Environmental factors in cardiovascular disease</title><secondary-title>Nature Reviews Cardiology</secondary-title></titles><periodical><full-title>Nature Reviews Cardiology</full-title></periodical><pages>627-642</pages><volume>12</volume><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>]. Epidemiological data at the population level has provided unequivocal proof that air pollutant exposure (e.g., ambient particular matter and NO_2) accelerates the development and progression of coronary atherosclerosis [ADDIN EN.CITE <EndNote><Cite><Author>Kaufman</Author><Year>2016</Year><RecNum>12</RecNum><DisplayText>(Kaufman et al., 2016)</DisplayText><record><rec-number>12</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468526230">12</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Joel D Kaufman</author><author>Sara D Adar</author><author>R Graham Barr</author><author>Matthew Budoff</author><author>Gregory L Burke</author><author>Cynthia L Curl</author><author>Martha L Daviglus</author><author>Ana V Diez Roux</author><author>Amanda J Gassett</author><author>David R Jacobs Jr</author><author>Richard Kronmal</author><author>Timothy V Larson</author><author>Ana Navas-Acien</author><author>Casey Olives</author><author>Paul D Sampson</author><author>Lianne Sheppard</author><author>David S Siscovick</author><author>James H Stein</author><author>Adam A Szpiro</author><author>Karol E Watson</author></authors></contributors><titles><title>Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study</title><secondary-title>The Lancet</secondary-title></titles><periodical><full-title>The Lancet</full-

title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. Xenobiotic metals such as arsenic, cadmium, lead, and mercury are also associated with atherosclerosis [ADDIN EN.CITE <EndNote><Cite><Author>Solenkova</Author><Year>2014</Year><RecNum>6</RecNum><DisplayText>(Solenkova et al., 2014)</DisplayText><record><rec-number>6</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468525712">6</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Natalia V. Solenkova</author><author>Jonathan D. Newman</author><author>Jeffrey S. Berger</author><author>George Thurston</author><author>Judith S. Hochman</author><author>Gervasio A. Lamas</author></authors></contributors><titles><title>Metal Pollutants and Cardiovascular Disease: Mechanisms and Consequences of Exposure</title><secondary-title>Am Heart J</secondary-title></titles><periodical><full-title>Am Heart J</full-title></periodical><pages>812-822</pages><volume>168</volume><number>6</number><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. Gene-environment interaction alters risk of vascular disease [ADDIN EN.CITE <EndNote><Cite><Author>Zanobetti</Author><Year>2011</Year><RecNum>2</RecNum><DisplayText>(Zanobetti, Baccarelli, & Schwartz, 2011)</DisplayText><record><rec-number>2</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468525348">2</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>A. Zanobetti</author><author>A. Baccarelli</author><author>J. Schwartz</author></authors></contributors><titles><title>Gene-air pollution interaction and cardiovascular disease: a review</title><secondary-title>Prog Cardiovasc Dis</secondary-title></titles><periodical><full-title>Prog Cardiovasc Dis</full-title></periodical><pages>344-352</pages><volume>53</volume><number>5</number><dates><year>2011</year></dates><urls></urls></record></Cite></EndNote>]; for example, the residential proximity to highways (representing exposure to a mixture of traffic-related air pollutants) is associated with peripheral

463 vascular disease, which is modified by the gene encoding bone morphogenic protein 8 [ADDIN
464 EN.CITE <EndNote><Cite><Author>Ward-
465 Caviness</Author><Year>2016</Year><RecNum>4</RecNum><DisplayText>(Ward-Caviness et
466 al., 2016)</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN"
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469 Ward-Caviness</author><author>Lucas M. Neas</author><author>Colette
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471 Abramson</author><author>Elizabeth Grass</author><author>Elaine
472 Dowdy</author><author>Robert B. Devlin</author><author>David Diaz-
473 Sanchez</author><author>Wayne E. Cascio</author><author>Marie Lynn
474 Miranda</author><author>Simon G. Gregory</author><author>Svati H.
475 Shah</author><author>William E. Kraus</author><author>Elizabeth R.
476 Hauser</author></authors></contributors><titles><title>Genetic Variants in the Bone
477 Morphogenic Protein Gene Family Modify the Association between Residential Exposure to
478 Traffic and Peripheral Arterial Disease</title><secondary-title>PLoS ONE</secondary-
479 title></titles><periodical><full-title>PLoS ONE</full-
480 title></periodical><volume>11</volume><number>4</number><dates><year>2016</year></d
481 ates><urls></urls></record></Cite></EndNote>]. Given the complexity of the drivers of
482 atherosclerosis, a medical model treating blood pressure and high cholesterol and advising
483 dietary modification and exercise will be inadequate to fully address this disease. Likewise
484 identifying the chemicals that increase risk on an individual basis will be inadequate to prevent
485 vascular disease. Instead an integrated systems approach is needed to fully account for all known
486 risk factors and formulate the problem to define the most effective strategy to decrease
487 individual risk and societal burden. Accomplishing this will require clinical data that fully reflects
488 a population under consideration as well as exposures to traditional risk factors, biomonitoring
489 data documenting exposures to multiple chemicals, and molecular responses from *in vitro* and *in*
490 *vivo* studies indicative of the activation of biochemical pathways that accelerate atherosclerosis.

While this approach might appear inconceivable, it is not unrealistic. Our proposed innovative approach to chemical risk assessment is occurring contemporaneously during the formative stages of the NIH-sponsored Precision Medicine Initiative that will drive integration of genomics, data sciences and bioinformatics as the basis for improved individual health care, disease prevention and public health. The Affordable Care Act has accelerated electronic medical record adoption within healthcare practices and hospital systems potentially offering a valuable source of information for population level health monitoring. Recent research has used Big Data to study the early stages of disease and better classify and predict disease progression and could be used to inform personalized medicine to optimize wellness in healthy populations [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Moreover, the anticipated integration and development of technologies and analytical tools have the potential to improve public health and increase the spatial and temporal resolution of environmental health surveillance. The establishment of a long-term representative precision medicine cohort, if integrated with the proposed National Biomonitoring Network [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Association of Public Health Laboratories (APHL)</Author><Year>2015</Year><RecNum>57</RecNum><Prefix>APHL </Prefix><DisplayText>(APHL 2015)</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472147337">57</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Association of Public Health Laboratories (APHL),</author></authors></contributors><titles><title>National Biomonitoring Plan. November 2015.</title></titles><dates><year>2015</year></dates><urls><related-urls><url>https://www.aphl.org/aboutAPHL/publications/Documents/EH_National_Biomonitoring_Plan_112015.pdf</url></related-urls></urls></record></Cite></EndNote>], could have enormous benefit in understanding the relationship between chemical exposures and disease and in managing some of the most challenging clinical problems more effectively. Applying this framework would potentially expand our understanding of the origins of vascular disease and its progression, help define strategies for primary prevention to thwart the initiation of the process we ultimately call atherosclerosis. Thus, such a framework will provide new and ongoing insights

into the associations between environmental exposures that contribute the greatest burden to public health. This approach would facilitate accounting for sensitive populations and could inform suggested individual health or behavioral measures where there has been past exposures or where current exposure cannot be reduced enough to protect those most at risk.

Discussion

The proposed conceptual model is grounded in public health principles and focused on identifying the greatest opportunity to reduce environmental exposures to improve health outcomes. Along with traditional risk assessment, this perspective can better inform public health decision making. While there are clear benefits to operating within a public health-focused framework and moving away from individual chemicals and apical endpoints, there are also challenges.

Informing decision-making: Since the 1980s, EPA's decision-making has been based on traditional risk assessments that are conducted within the constraints of EPA's statutes and programs. While program-targeted risk assessments will remain an important component, the disease-based approach draws upon information in a holistic fashion that cuts across organizational and legal boundaries, integrating traditional inputs with newer data streams. These assessments will provide decision-makers with critical information to inform exposure reduction efforts to impact the selected health outcomes, and ultimately, improve public health. Because those exposure reduction efforts would take place within the existing statutory construct, an important implementation step would be to move from findings of disease-based risk assessments to assessments of specific risk management actions under the relevant statutory authorities.

Priorities for screening and testing: A health outcome-focused framework can inform priorities for screening and testing the toxicity of chemicals. Efforts to develop and synthesize approaches for screening large numbers of chemicals using high-throughput toxicity testing and exposure prediction should continue to provide data for data-poor chemicals. For example, in the recently announced Cancer Moonshot [ADDIN EN.CITE <EndNote><Cite><Author>Mitchell</Author><Year>2016</Year><RecNum>40</RecNum><Dis

playText>(Mitchell, 2016)</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470324343">40</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Edith Mitchell</author></authors></contributors><titles><title>Moonshot Toward a Cure for Cancer</title><secondary-title>Journal of the National Medical Association</secondary-title></titles><periodical><full-title>Journal of the National Medical Association</full-title></periodical><pages>104–105</pages><volume>108</volume><number>2</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>], high-throughput approaches could screen a large set of chemicals for potential carcinogenicity and identify a suite of chemicals for additional animal toxicity testing. Examining noncancer endpoints may also be challenging, which is why developing AOPs and networks to contextualize and interpret non-apical hazard data in relation to population health is of increasing value. Epidemiology studies can be designed to inform and validate high-throughput testing approaches by identifying both chemical stressors and nonchemical stressors that modify responses to chemical exposures and also to test relationships between disease and early markers of exposure and biological response (e.g., epigenetic changes).

Better understanding the impact of cumulative exposures: While cumulative risk assessment has been of high interest for the past few decades, putting cumulative assessment approaches into practice has been challenging. This framework provides a new construct for considering cumulative risk. By focusing on a health endpoint of concern, one could consider the multiple exposures that may contribute to a health outcome. Past NRC recommendations have encouraged assessors to evaluate the combined effects of exposures to all chemicals that affect a common adverse outcome, for example, male reproductive development [ADDIN EN.CITE <EndNote><Cite><Author>National Research Council</Author><Year>2008</Year><RecNum>9</RecNum><DisplayText>(National Research Council, 2008)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs"

timestamp="1468525915">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>National Research Council,</author></authors><tertiary-authors><author>The National Academies Press,</author></tertiary-authors></contributors><titles><title>Phthalates and Cumulative Risk Assessment: The Tasks Ahead</title></titles><dates><year>2008</year></dates><pub-location>Washington, D.C.</pub-location><urls></urls></record></Cite></EndNote>]. Challenges include gaining adequate understanding of individual chemical impacts in order to group chemicals by health outcome. Increased research into the biological pathways by which chemicals affect health status can help inform approaches for estimating the joint effect of chemicals without testing all permutations or combinations.

One possible example of an alternative approach is Health Impact Assessment (HIA), which uses a systems approach to array data sources and analytic methods and considers input from stakeholders to determine potential effects of a proposed action or decision on the health of a population and the distribution of those effects within the population [ADDIN EN.CITE <EndNote><Cite><Author>National Research Council</Author><Year>2011</Year><RecNum>41</RecNum><DisplayText>(National Research Council, 2011)</DisplayText><record><rec-number>41</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470324571">41</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>National Research Council,</author></authors><tertiary-authors><author>The National Academic Press,</author></tertiary-authors></contributors><titles><title>Improving Health in the United States: The Role of Health Impact Assessment</title></titles><dates><year>2011</year></dates><pub-location>Washington, D.C.</pub-location><urls></urls></record></Cite></EndNote>]. Using HIA approaches for chemical risk assessments done through this framework can offer a method to organize various data streams that can influence our understanding of a health impact, inform potential multiple

contributors to adverse health outcomes, and provide recommendations to decision makers on monitoring and managing these outcomes.

Consider public health concepts such as attributable or relative risk: This new approach takes a systematic view of collective factors that contribute to a health outcome or disease state, including those that are not regulated by one single federal entity. Any single health outcome may be influenced by multiple factors beyond chemical exposures, such as nutrition, genetics, or social stressors. Because those factors are not regulated, it is important for environmental regulatory agencies to understand what fraction of the disease burden is influenced by the regulated environmental exposure. Public health approaches, such as attributable risk, can help inform this understanding. Challenges may include incorporating these approaches, which are typically used in epidemiology, to animal and advanced toxicity testing data, ensuring adequate training with the approaches, and communicating risk in a way that acknowledges the influence of non-regulated factors.

Conclusions

Understanding the health effects of chemicals has real implications for public health. This proposed approach for chemical risk assessment starts at the health endpoint and incorporates multiple data streams, including data developed using newer technologies such as high-throughput screening. In parallel with more traditional risk assessment approaches, this will lead to a better understanding of mechanisms of single chemicals as well as cumulative exposures that lead to specific disease endpoints. This new lens will need to be applied to the complete risk assessment process, including problem formulation, data considerations, and data synthesis through multi-pathway methods, including cumulative assessment and health impact assessment, with an eye to prevention of adverse effects. This approach draws upon the best available science to improve our understanding of the health impacts of environmental chemicals and informs decision making to prevent, reduce, or mitigate exposure and ultimately improve public health.

633 **References**

634 [ADDIN EN.REFLIST]

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Figure Legends

Figure 1. Conceptual Model for a Public Health Perspective for Chemical Risk Assessment

This conceptual model illustrates how the starting point in a public-health focused risk assessment would differ from that of traditional risk assessment. In traditional risk assessment, the starting point is focused on specific chemicals or classes of chemicals of concern, with multiple data streams informing what are the critical effects from that chemical. A public health perspective would focus on the adverse health outcome of concern with multiple data streams informing our understanding of hazard and exposure in the context of public health decisions related to that outcome, and not necessarily focused on just one chemical or class of chemicals.

Figure 2. Adverse Outcome Pathway for Cardiovascular Outcomes. This figure illustrates the biological pathway leading from exposure to adverse cardiovascular outcomes for a variety of chemicals. On the left hand side of the figure these pathways are linked to the AOP whereas on the right hand side of the figure we see the traditional risk factors for adverse cardiovascular outcomes. Action of specific chemicals and metals adapted from Kirkley AG and Sargis RM Curr Diab Rep 2014.